Breast Cancer Survivors, Common Markers of Inflammation, and Exercise: A Narrative Review

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ABSTRACT: Exercise may help positively improve inflammatory marker levels, therefore promoting better outcomes in breast cancer survivors. This narrative review is intended to provide an overview between inflammation and breast cancer, in addition to the effects exercise may have on common inflammatory markers that have been examined in both healthy populations and breast cancer survivors throughout the literature. The inconsistencies and gaps in the literature addressed may be important for future research to further understand the relationship between exercise and inflammation, as well as the underlying biological mechanisms that are responsible for these changes. For the purpose of organization, this review is structured into the following sections: (1) Breast Cancer Facts, Treatment-Related Side Effects, and General Exercise Benefits; (2) Effects of Exercise on Markers of Inflammation in Cancer-Free Populations; (3) Cancer and Markers of Inflammation; (4) Effects of Exercise on Markers of Inflammation in Breast Cancer Survivors; and (5) Conclusions.

KEYWORDS: Breast cancer survivors, inflammation, exercise

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Breast Cancer Facts, Treatment-Related Side Effects, and General Exercise Benefits

Breast cancer facts

Breast cancer is defined as a malignant tumor starting in the cells of the breast that may metastasize to distant areas of the body or invade surrounding tissues. Except for skin cancers, breast cancer is the most commonly diagnosed cancer and the second-leading cause of cancer death in women in America. In 2017, it is estimated that approximately 252,710 new cases will be diagnosed along with 40,610 deaths among women from breast cancer in the United States.[1]

Breast cancer treatment primarily consists of surgery, chemotherapy, radiation therapy, hormone therapy, and targeted therapy. The method of administration depends on the type and stage of the breast cancer, and many of these treatments are combined according to the needs of the patient. Common surgical treatments are used to remove cancer from the breast and may include lumpectomy, partial mastectomy, or total mastectomy. Chemotherapy, radiation, and hormone therapy treatments are used either to help prevent cancer cell division and growth or to destroy cancer cells completely.[2] Targeted therapies are also being developed that are tumor specific. These types of therapies are growing in number and include trastuzumab, also known as Herceptin, which is a monoclonal antibody given to breast cancer survivors who overexpress the protein called human epidermal growth factor receptor 2 (HER2/neu receptor) that is responsible for promoting the growth of cancer cells.[3]

Breast cancer treatment–related side effects

Breast cancer survival rates have improved due to earlier detection through increased awareness and screening, advancements in modern technology, increased self-examination, and improvements in treatment.[4] Although survival rates have increased in the past several years, many negative adverse side effects can result from breast cancer treatment. Treatment-related side effects may be acute, lasting over a period of days or weeks, or they may be persistent, lasting years after the completion of treatment. Pain, infection, tenderness, bleeding, and temporary swelling are among the side effects of surgical treatment for breast cancer. Chemotherapy side effects may include weight changes, nausea, hair loss, fatigue, vomiting, and an increased chance of infections. Radiation treatments may cause patients to encounter soreness, fatigue, skin changes, and swelling. Side effects of hormone therapy may involve hot flashes, fatigue, vaginal discomfort, and mood swings.[3]

Overall, usual side effects observed in patients with cancer who have undergone treatment are depression, worry, pain, cachexia, dyspnea, nausea, and fatigue.[5] Studies have reported that 70% of patients undergoing chemotherapy and radiation have fatigue.[6] Both radiation and chemotherapy have also been shown to cause necrotic death of cancer cells and surrounding tissues, which can result in increased inflammation in patients with breast cancer.[7]

Exercise benefits on breast cancer risk reduction and treatment-related side effects

An association has been reported between higher levels of inflammatory markers and breast cancer risk, specifically with increased markers such as C-reactive protein (CRP)

and interleukin 6 (IL-6).[8–10] Not all studies have found a significant inverse association between physical activity and breast cancer risk, specifically risk of postmenopausal breast cancer.[11] However, strong evidence has been found in epidemiologic studies that exercise is significantly associated with breast cancer risk reduction.[12] In a systematic review conducted by Friedenreich, 73 epidemiologic studies were reviewed providing evidence that physical activity reduces breast cancer risk by about 25%.[13] In addition, physical activity either before or after breast cancer diagnosis has been shown to be associated with a reduction in both breast cancer-specific mortality and all-cause mortality, with some evidence suggesting a dose-response effect of decreased mortality risk with increased activity levels.[12,14,15] Exercise may also improve overall general health, and studies have shown that exercise can be a helpful tool in attenuating the physiological effects associated with breast cancer treatment. Improvements in cardiorespiratory fitness, body composition, physical functioning, quality of life, and fatigue have been shown by systematic review evidence in cancer survivors who exercise.[16,17]

Patients receiving cancer treatments in previous years were advised to rest and avoid activity known to further decrease energy levels. Exercise has been shown by scientific research to help alleviate the routine symptoms of cancer treatments such as pain, nausea, and fatigue. Possible benefits of exercise used to alter normal cancer treatment side effects include improved cardiovascular efficiency, increased mobilization, muscle regeneration, energy production enhancement, and stimulation of erythrocyte, leukocyte, and thrombocyte cell production.[5] Numerous studies have generally demonstrated that exercise does indeed reduce insulin resistance, endogenous estrogen levels, adiposity levels, and inflammation.[13]

Effects of Exercise on Markers of Inflammation in Cancer-Free Populations

Exercise and inflammatory markers

Exercise modulates the immune system in healthy individuals and can work as a model of temporary immunosuppression.[18] The inflammatory regulation of exercise has been linked to the production of cytokines.[19] Cytokines are released at the site of inflammation as a result of exercise, infection, or tissue injury. The exercise-induced local inflammatory response is accompanied by a systemic response known as the acute-phase response.[18,20] This response includes the production of a large number of hepatocyte-derived acute-phase proteins, such as CRP.[19]

Although many different cell types produce plasma cytokines, muscle cells are a major source during exercise.[21] Muscle contractions can induce a myokine response, which is characterized by the release of cytokines, such as IL-6, from working muscles. Regular muscle contraction can mediate signals with myokines that may suppress pro-inflammatory activities at both distant sites and within the skeletal muscle itself.[22,23]

The cytokine response in relation to exercise may be initiated due to the mechanical disruption of myofibers. The production of cytokines resulting from exercise resembles that observed in relation to trauma. However, many of the effects that come with the fully developed, systemic pro-inflammatory response occurring with trauma do not happen with exercise. Although the initiation of the acute-phase response develops, the lack of a fully developed systemic response with exercise may be due to exercise only resulting in a transient release of cytokines.[18] Increases in pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) are minute due to exercise without muscle damage. This indicates that in nontraumatic exercise, the cytokine cascade differs importantly from the classical acute-phase response in infectious systems.[22] The fact that pro-inflammatory cytokines such as TNF-α may not increase with exercise provides evidence for the difference in the cytokine response to exercise compared with that of severe infections.[19] Also, anti-inflammatory cytokines, soluble receptors, and receptor antagonists can restrict the inflammatory response to exercise, potentially having an effect on exercise not producing a full systemic response.[20]

Numerous studies have shown that several cytokines can be found in plasma both during and after exercise. Although acute exercise protocols result in short-term changes in particular cytokines, chronic exercise training may result in decreased levels of many circulating cytokines.[21] Exercise may also induce an increase in the systemic levels of a number of cytokines with anti-inflammatory properties and thereby can protect against chronic medical disorders associated with low-grade systemic inflammation.[19] The mechanisms of inflammatory marker changes that are influenced by exercise may potentially be related to effects on endothelial cells, muscle tissue, and immune cells.[24]

Exercise in relation to the inflammatory process

Epidemiologic evidence supports the notion that a lifestyle with a high degree of physical activity is associated with attenuated circulating levels of TNF-α, IL-6, and CRP independent of age, sex, body mass index (BMI), or blood glucose. Furthermore, a high level of physical activity is associated with reduced levels of peripheral inflammatory mediators in the range of 20% to 60% compared with a sedentary lifestyle.[22] Physical inactivity has even been shown to be associated with low-grade systemic inflammation in healthy persons according to several observational studies.[19] In cancer-free individuals, elevated levels of CRP may be associated with increased body fat and sedentary lifestyles.[25] Overall, multiple studies have found a strong inverse relationship between physical fitness and markers of inflammation.[26–28]

More frequent physical activity may help reduce the levels of systemic inflammation in the general population. Both randomized controlled trials and cross-sectional reports using noncancerous samples have indicated that increased levels of

exercise are associated with decreased levels of inflammatory markers such as CRP.[29–32] Abramson and Vaccarino found that a higher frequency of physical activity was independently associated with lower odds of having elevated inflammation levels, such as CRP and white blood cell count, among healthy middle-aged and older US adults. This association was found even after adjustments were made for potential confounding factors including measures of general obesity (BMI) and central obesity (waist-to-hip ratio), which have been shown to influence levels of inflammation.[29] Also, physical activity has been shown to be inversely associated with CRP concentrations in a representative sample of healthy adults in the United States, suggesting that physical activity may mitigate inflammation.[33]

Even light to moderate physical activity has been shown to be associated with lower blood concentrations of inflammatory markers, especially in cross-sectional designs. Specifically, Pitsavos et al[34] found that leisure time physical activity was associated with 33% lower concentrations of CRP and 10% lower concentrations of white blood cell counts independent of age. Also, only 30 minutes of moderate exercise on a regular basis may have the ability to facilitate an anti-inflammatory environment represented by enhanced levels of cytokines such as interleukin 10 (IL-10).[22]

There have been randomized controlled trials examining the dose-response of exercise interventions on inflammatory markers in postmenopausal women. In the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial, Friedenreich et al[31] showed that a 1-year aerobic exercise intervention decreased circulating CRP, IL-6, and TNF-α levels compared with usual inactive lifestyles, and increased exercise volume was associated with significant linear trends of decreasing levels of these biomarkers. Friedenreich and colleagues also implemented a yearlong randomized dose comparison trial with postmenopausal women to examine whether higher exercise volume resulted in a larger decrease in certain markers of inflammation. The study found no significant improvements in CRP, IL-6, or TNF-α regarding higher exercise volume (300 minutes of moderate-to-vigorous aerobic exercise per week) compared with lower exercise volume (150 minutes of moderate-to-vigorous aerobic exercise per week). However, in considering the overall effect of exercise time, the investigators did find a significant trend of decreased CRP levels with increased exercise time. The authors stated that exercise intensity, in addition to dose, is relevant when determining the impact of exercise on markers of inflammation, although there is limited research on the relationship between exercise intensity and changes in biomarkers.[23] Higher exercise intensity has been associated in some observational studies with reduced levels of CRP, IL-6, and TNF-α.[34,35] According to these findings, longer periods of vigorous exercise may reduce chronic inflammation more effectively. It should be noted, however, that throughout the literature, physical activity has not been shown to consistently mitigate symptoms associated with menopause.[36]

Because adipose tissue is known to be a source of pro-inflammatory cytokines, decreasing adiposity can lead to lower levels of circulating cytokines.[37,38] However, multiple studies indicate that the association between exercise and inflammation is not entirely mediated by reductions in obesity, and other mechanisms such as the antioxidant effects of exercise may be involved in the relationship between exercise and decreasing levels of inflammation.[29,39–41] It is possible that exercise training in general may reduce markers of inflammation, such as CRP, both directly and indirectly. Exercise may reduce CRP directly by reducing cytokine production in muscle, fat, and mononuclear cells and indirectly by reducing body weight, increasing insulin sensitivity, and improving endothelial function.[42] Multiple studies have found an association between exercise and inflammation, but the exact mechanisms through which physical activity influences the inflammatory process are not all well understood.[15,24,33]

Exercise-induced anti-inflammatory response

Several studies have shown that physical activity mediates strong anti-inflammatory effects in skeletal muscle and fat tissue. Exercise has the ability to produce acute increases in various anti-inflammatory mediators.[42] The anti-inflammatory effects of exercise have been attributed to mechanisms that involve the cytokine IL-6.[22,43] Interleukin 6 can increase as much as 100-fold after strenuous exercise, and this increase is the earliest as well as the most prominent cytokine response to exercise.[42] There is controversy over whether IL-6 has pro-inflammatory or anti-inflammatory properties, but some studies suggest that IL-6 should be classified as an anti-inflammatory cytokine due to the fact that IL-6 may stimulate the production of IL-10 and the interleukin 1 receptor antagonist protein (IL-1ra) while inhibiting the production of TNF-α. Interleukin 6 has also been found to enhance the levels of both IL-10 and IL-1ra, independently of TNF-α.[43,44]

Starkie et al found that physical activity may mediate anti-inflammatory activity, and exercise-induced IL-6 production may help to mediate the effect of exercise on TNF-α production. Eight healthy subjects received an endotoxin bolus to induce low-grade inflammation after 2.5 hours into a 3-hour bout of exercise on a cycle ergometer. Increases in TNF-α from the endotoxin bolus were totally attenuated due to the exercise, whereas the endotoxin induced a 2-fold to 3-fold increase in circulating levels of TNF-α during rest in the same subjects. There are potentially other mediators, such as epinephrine, that may contribute to the anti-inflammatory effects of exercise as well. Epinephrine is highly induced by exercise and has the ability to blunt the appearance of TNF-α production.[44] The finding that exercise suppresses TNF-α production has also been supported in animal models in which exercise normalized the overexpression of TNF-α in TNF receptors 1 and 2 knockout mice.[45]

In a 2005 review article by Petersen and Pedersen, circulating levels of anti-inflammatory cytokines were commonly found in relation to exercise. As a result of exercise, increases primarily in IL-6 followed by increases in IL-1ra and IL-10 have been thoroughly reported.[19] The production of IL-10 that has been shown with exercise can lead to inhibition of the synthesis of a large range of pro-inflammatory cytokines by different cells, notably of the monocytic line of descent. Therefore, IL-10 may be able to inhibit the production of TNF-α by attenuating the surface expression of TNF-α receptors.[19,43] Interleukin 10 may also be able to inhibit the production of interleukin 1α and interleukin 1β as well as the production of some chemokines. The anti-inflammatory effects of an acute bout of exercise may protect against chronic systemic low-grade inflammation, but a similar link between the acute effects of exercise and long-term benefits has yet to be determined.[19]

Simultaneous increases in both pro-inflammatory and anti-inflammatory markers due to exercise

Exercise may induce an increase in pro-inflammatory cytokines, such as TNF-α. This release of pro-inflammatory cytokines may also be balanced by the release of cytokine inhibitors and anti-inflammatory cytokines, such as IL-10. These findings suggest that anti-inflammatory cytokines as well as cytokine inhibitors may restrict both the duration of the exercise and the exercise-induced inflammatory response.[18,20] Therefore, there is a parallel anti-inflammatory counter-regulation that is also part of the acute-phase response to exercise.[42,46]

Ostrowski et al found a significant increase in TNF-α after a strenuous bout of exercise (marathon) in healthy adult men. Significant increases in the inflammation responsive cytokine IL-6 were also found following the exercise with only a modest increase in plasma CRP. Both anti-inflammatory cytokines (IL-10) and cytokine inhibitors were significantly increased due to the exercise, serving to balance the exercise-induced release of pro-inflammatory markers.[20] Contraction-induced IL-6 expression may be followed by a systemic anti-inflammatory response, providing a common underlying pathway by which pro-inflammatory markers (TNF-α activity) are attenuated after a single bout of exercise.[22] Although strenuous exercise has been shown to result in positive changes in inflammatory markers, high-intensity exercise, prolonged bouts of strenuous exercise, or exercise in an immunosuppressed state may induce a negative inflammatory state as well as immunosuppression.[47–50] This phenomenon, called the "open window theory" describes a period of time after exercise in which an individual may be subject to increased risk of infection due to a depression in immune function. "Over-trained" states may result in the depression of key immune parameters, which have been linked to imbalances in cytokines.[48]

Even though strenuous exercise has been shown to induce an initial pro-inflammatory and anti-inflammatory response, there may be a different effect as a result of moderate exercise in healthy individuals. Markovitch et al found that acute moderate-intensity exercise had no effect on pro-inflammatory or anti-inflammatory responses. Twelve sedentary men underwent 30 minutes of walking at 50% VO_{2max} in which no significant changes were found in CRP, IL-6, or IL-10 concentrations over the 7 days following the single bout of exercise. The results from this study may suggest that the long-term anti-inflammatory effects that were previously reported with exercise of moderate intensity must be explained by something other than a net anti-inflammatory response to each exercise bout.[26]

Variability found in the levels of inflammatory markers across studies

There have been many differences found between markers of inflammation due to exercise. Inconsistent findings have been reported for TNF-α, IL-6, and CRP in response to exercise.[15,20,32] There are several possible explanations for these variable results on cytokines in relation to exercise including the following: (1) the intensity and duration of the exercise as well as the type of physical activity, (2) the specificity and the sensitivity of the assays used in particular studies, (3) heterogeneity of subjects from sample to sample, (4) varying sample sizes, and (5) different assessments of physical activity and exercise behaviors. Increased cytokine levels have mainly been described due to eccentric training, but concentric exercise can induce cytokine production as well. Also, the magnitude of the increases found in markers of inflammation may be closely related to the duration of the exercise.[18,36,46] Very few studies have examined the inflammatory response due to acute moderate-intensity exercise, and the findings are controversial. Although some studies have found increases in inflammatory markers due to acute moderate-intensity exercise, others have found no changes in these markers.[26,51]

Cancer and Markers of Inflammation

Cancer and inflammation

Increased circulating levels of inflammatory markers are known to be associated with cancer, and large cohort and cross-sectional studies have observed a strong association between chronic inflammation and some types of cancer.[52–54] Inflammatory cells may have powerful effects on tumor development, and inflammation has been shown to act as a tumor promoter. Inflammation can affect tumor development and progression in addition to the response to therapy.[7,55] Cytokines are mediators that govern a vast range of processes involved in the development of cancer, and markers of inflammation form a major part of the tumor microenvironment.[56] Inflammatory cells as well as cytokines regulate the entire tumor organ, managing the migration, growth, and differentiation of all types of cells in the tumor microenvironment.[57] These cytokines can also influence immunosuppression and tissue remodeling in

the inflammatory microenvironment, which is a critical component of all tumors.[7,52]

An irregular balance between pro-inflammatory and anti-inflammatory mechanisms often occurs in the cancer population, leading to chronic inflammation as well as chronic immune activation.[52] Cytokines such as TNF-α may play a role in tumor progression by producing an optimal environment for tumor growth, promoting angiogenesis, and assisting genomic instability.[57] Tumor growth initially depends on increased cell proliferation and reduced cell death, both of which are stimulated by inflammation-driven mechanisms. Tumor promotion that is induced by inflammation may occur early or late in tumor development.[7] A common view about the cause of cancer is that inflammation may promote cancer, but recent evidence has shown that cancer may cause inflammation. Cancer-induced inflammation may be due to the activation of intrinsic inflammation pathways by genetic events that cause neoplasia.[56]

Recruitment of inflammatory markers may also interfere with tumor development and mediate the suppression of tumor growth. Although inflammatory responses may also be antitumor, patients with cancer often have abnormal inflammatory responses.[58] These abnormal responses may arise from two different mechanisms: failure to upregulate anti-inflammatory cytokines and disruption of the host response from the desensitization of receptors. The latter of the two mechanisms may lead to increased cytokine concentrations, attenuating systemic responses.[57] The development of malignancy in some cancers may be preceded by inflammatory conditions, whereas other cancers may have oncogenic changes driving a tumor-promoting inflammatory environment. Regardless of the origin, this inflammation may aid in the growth and survival of malignant cells, angiogenesis, and metastasis. In addition, responses to hormones and chemotherapy drugs may be potentially altered.[56]

Pretreatment markers of inflammation in patients with breast cancer

Before surgery, patients with breast cancer have been shown to exhibit elevated levels of CRP, with higher stages of breast cancer resulting in even larger concentrations of CRP. This may insinuate that CRP is related to tumor progression in these patients.[59] Also, high levels of the cytokine IL-6 has been shown to potentially be a predisposing genetic factor contributing to worse breast cancer prognosis.[60,61] It has been found that cancer survivors with chronic inflammation may have an overall higher risk of recurrence due to the effects of the inflammatory processes on cell growth.[59]

Altered inflammatory responses occur frequently in women with breast cancer, and studies have related breast cancer to an inflammation etiology.[58] It has been reported that CRP, TNF-α, and IL-6 are elevated in patients with breast cancer.[52] As previously mentioned, IL-6 has been found to correlate with both cancer stage and degree of metastasis as well as breast cancer recurrence.[60] Also, increased CRP levels may be associated with mortality in women diagnosed with breast cancer.[62]

Breast cancer treatments and inflammation

Surgery, chemotherapy, and radiation can all induce local or systemic increases in inflammation.[63] Surgery may result in tissue injury through the activation of stress-sensing pathways. Chemotherapy and radiation may result in cancer cell death through necrosis, which is a pro-inflammatory form of cell death.[7] Different cancer treatments can activate the immune system to generate pro-inflammatory cytokines that have been associated with toxic effects of treatment, such as bone loss, flu-like effects, and fatigue. Increases in this category of cytokines have also been related to cachexia, pain, and resistance to treatment in patients with cancer.[52] Cancer and some of its treatments can encourage an upregulation of pro-inflammatory cytokines in which many of these cytokines may promote a metabolic state or other condition that results in tissue losses.[64] There is also growing evidence that links inflammation and fatigue both during and after cancer treatment. Chemotherapy has been associated with acute increases in markers of inflammation as well as fatigue, which may last long into survivorship.[65]

However, chemotherapy and radiation may be used to eliminate the tumor-promoting inflammatory microenvironment by causing the death of tumor-promoting immune/inflammatory cells.[7] Activation of the immune system by cancer treatments might also have a role in producing anticancer effects by differentially altering the secretion of cytokines. Although cancer treatments attempt to reduce markers of inflammation, most of the breast cancer survivors have been shown to display increased levels of inflammation compared with healthy women.[52]

Breast cancer survivors and higher levels of inflammation

Survivors of breast cancer have been shown to have higher levels of circulating cytokines and receptors than their healthy counterparts.[52,53] Systemic inflammation has been shown to potentially be an important long-term prognostic factor for breast cancer. A significant association has been found between reduced overall survival and increased concentrations of inflammatory markers, such as CRP.[14,59] According to Seruga et al[52] preliminary data indicate that circulating levels of different cytokines are significantly higher in breast cancer survivors up to 5 years after diagnosis than in healthy controls. Measurement of percent body fat has been found to be the most important predictor of inflammatory markers in breast cancer survivors. Increased body fat may be associated with increases in inflammation, and considering that many breast cancer survivors are overweight or obese, increased body fat could cause additional problems in the inflammatory

microenvironment of these patients.[25,38] In addition, breast cancer mortality rate has been shown to be increased with weight gain after diagnosis.[38] It has been reported that more than 50% of breast cancer survivors are overweight or obese, and the breast cancer survivors who gain weight may have increased levels of inflammation.[62] With weight gain, fat cells in the breast expand and are more likely to die. The death of these cells may trigger the release of saturated fatty acids, which activate macrophages. Fatty acids that bind to the receptors of macrophages may start the cascade of inflammation by triggering the production of interleukin 1, IL-6, and TNF-α.[66]

Breast cancer survivors with higher stages of breast cancer and metastases may have higher levels of pro-inflammatory cytokines than those with lower stages and nonmetastatic cancer.[53] Higher levels of pro-inflammatory cytokines may be a primary cause of fatigue in these patients because persistent fatigue has been associated with increased levels of these inflammatory markers in breast cancer survivors.[52] Findings have suggested that TNF-α may play a significant role in chemotherapy-induced fatigue. Also, animal models have shown that chemotherapy-induced rises in TNF-α have led to increased oxidative stress and inflammation in the brain.[65] Considering fatigue is one of the most common side effects experienced among breast cancer survivors, the reduction in pro-inflammatory cytokines may be essential in improving their quality of life.[52] Likewise, poor survival outcome in patients with breast cancer has been associated with low expressions of certain anti-inflammatory cytokines, such as IL-10. Improvements in these levels may help ameliorate prognosis and life expectancy in breast cancer survivors.[67]

Potential reasons for elevated inflammation in breast cancer survivors

It has been noted that future cancer therapies should focus on normalizing the inflammatory network to re-establish an overall normal host response.[57] The occurrence of therapy-induced inflammation is possible, and the various forms of therapy that can induce the death of malignant cells may activate cytokine-producing inflammatory cells.[7] Current cancer treatments may not be able to completely diminish the high levels of tumor-promoting mediators, such as pro-inflammatory cytokines, while increasing tumor-suppressing factors, such as anti-inflammatory cytokines.[56] The destruction of tumor cells has been the concentration of cancer treatments for many years. Proposed strategies to moderate the host microenvironment offer supplemental approaches to cancer treatment, and cancer-associated inflammation may be an interesting target of antitumor therapies in the future.[61,68]

Inhibiting antibodies that have been shown to have a significant therapeutic effect in other inflammatory diseases may be applicable to cancer therapies.[57] Even though cancer therapies attempt to reduce inflammation, this is not always successful and may be one of the reasons why many cancer survivors have elevated levels of inflammation. In some instances, inflammation has been shown to diminish the beneficial effects of cancer therapy.[55] Also, cancer therapy, such as chemotherapy and radiation, may cause a strong tumor-associated inflammatory response due to the necrotic death of cancer cells and surrounding tissues that can occur with these types of treatments.[7]

Discussions about the breast cancer population and inflammation in different studies allude to possible causes, but mechanisms as to why breast cancer survivors have increased inflammation are speculative as of now. Although it is evident that inflammatory processes may have a role in the progression of tumors, not much is known about why these survivors still have increased levels of inflammation after cancer treatment.[7] The following are possible mechanisms for why this is occurring: (1) treatment-related increases in inflammation with muscle and tissue damage due to cancer treatments and (2) treatments potentially not being able to alleviate inflammatory markers that could have led to metastasis in the first place.[68,69] How far the cancer progression was in each patient before treatment could potentially be a big determinant in how well the treatment can decrease and return levels of inflammation to normal in the breast cancer population.[53]

Effects of Exercise on Markers of Inflammation in Breast Cancer Survivors

Exercise and inflammation in breast cancer survivors

Inflammatory markers that have been commonly measured in this population throughout the exercise oncology literature include TNF-α, CRP, interleukin 2 (IL-2), IL-6, and IL-10. It has been suggested by several studies that physical activity is associated with a modest decrease in mortality for the patients with breast cancer.[12-15,59] In observational studies, better lifestyle choices including moderate-intensity exercise have resulted in improved survival after treatment of patients with breast cancer.[52,70] It is evident that appropriate amounts of physical activity may promote an upregulation of anti-inflammatory cytokines while downregulating the expression of some pro-inflammatory cytokines, positively modulating the tumor microenvironment. Preliminary findings support this shift in a healthier inflammatory cytokine profile with physical activity in patients with cancer. As a result, this may lead to improved muscle tissue status as well as an acceleration of protein synthesis within the skeletal muscle.[64] Several exercise trials with breast cancer survivors have found reductions in both pro-inflammatory markers and adiposity, and it has been postulated that physical activity's effects on cytokine levels may be mediated through fat loss.[13,38,62]

Exercise has been shown to reduce inflammatory markers, such as CRP, independent of changes in body fat due to the modification of cytokine production at nonadipose sites such as mononuclear cells and skeletal muscle. Reductions in inflammatory markers with exercise may occur indirectly through

improved endothelial function, reduced body weight, or increased insulin sensitivity.[25] The potential anti-inflammatory effect of physical activity could explain the better outcome of cancer found in observational studies. Cumulative anti-inflammatory effects of repeated exercise bouts could be one of the mechanisms responsible for the health benefits of regular exercise.[53] A physically active lifestyle has been shown to decrease production of pro-inflammatory cytokines in noncancer populations and has been reported to improve blood immune function in breast cancer survivors. Increasing evidence suggests that exercise may be an important part of the lifestyle of breast cancer survivors in improving treatment-related fatigue as well as preventing cancer recurrence and death.[12,14,52]

Specific studies examining exercise and inflammatory markers in breast cancer survivors

Summarized descriptions and common inflammatory marker outcomes in breast cancer survivors of the specific exercise studies explored in this review are presented in Table 1.

Fairey et al examined the effect of an exercise intervention on markers of inflammation in breast cancer survivors. In total, 53 postmenopausal breast cancer survivors were randomized into either a control (n = 28) or exercise group (n = 25) in which the subjects in the exercise group trained on cycle ergometers 3 times per week for 15 weeks. The researchers found no significant changes between the groups in cytokine production by blood mononuclear cells. In addition, CRP decreased by 1.39 mg/L in the exercise group, whereas it increased by 0.10 mg/L in the control group. Although the mean between group change in CRP was −1.49 mg/L, the exercise training was found to have a change in CRP that only approached significance ($P = .066$). Even though the study did not find changes in cytokine production, the authors did find significant improvement in blood immune function due to the exercise training with an increase in natural killer cell cytotoxic activity.[71,72]

Hutnick et al were interested in the effect of a 6-month exercise intervention on both inflammatory and immune function markers in posttreatment patients with breast cancer. The study consisted of two groups: an exercise group (n = 28) and a nonexercise control group (n = 21). Subjects in the exercise group underwent combined aerobic and resistance training sessions 3 times per week, but 12 of these subjects participated in the exercise training for only 3 months instead of the full 6 months. The exercise group had higher but nonsignificant levels of IL-6 throughout the exercise program compared with the control group. Although there were no significant changes found in cytokines throughout the exercise intervention, there were greater levels of lymphocytes, such as $CD4^+$ cell activation, found in the exercise group. These findings suggest that a moderate-intensity exercise program may result in an increased immune system function in breast cancer survivors.[60]

Payne et al also reported no effect of physical activity on circulating levels of IL-6. The study examined the effect of a prescribed home-based walking exercise intervention (n = 10) versus usual care (n = 10) on IL-6 in older women (aged 55 years or older) receiving hormonal treatment for breast cancer. The intervention consisted of a moderate walking activity, 20 minutes in duration, 4 times a week for 14 weeks. IL-6 was measured at the initial clinic visit and again at 12 weeks in both groups. No significant differences were found in IL-6 levels between groups or over time.[73]

Gómez et al found no significant changes in TNF-α, IL-10, or IL-6 among other cytokines in breast cancer survivors after a combined aerobic and resistance exercise training program. The breast cancer survivors underwent 3 sessions per week for a total of 8 weeks. The training program was not able to decrease circulating levels of pro-inflammatory cytokines or increase levels of major anti-inflammatory cytokines. However, the authors did observe a decrease in the IL-10/TNF-α ratio in these subjects due to the exercise that approached significance. The authors noted that the decrease found in the IL-10/TNF-α ratio might indicate that the exercise intervention did have an anti-inflammatory effect on the breast cancer survivors. The research team then went on to suggest that perhaps a more intense or longer exercise intervention may be necessary to induce a significant anti-inflammatory benefit.[53]

The effect of resistance training on inflammatory markers has also been examined in breast cancer survivors. Hagstrom et al randomly assigned 39 breast cancer survivors to a resistance training group (n = 20) or nonexercise usual care control group (n = 19). The resistance training group underwent supervised exercise 3 times per week for 16 weeks. Markers of inflammation (serum TNF-α, IL-6, IL-10, and CRP) were measured before (week 0) and after the 16-week period (week 17) in both groups. No significant changes between groups were found for any of the inflammatory markers. Nonetheless, there was a significant reduction observed in the exercise group compared with the control group for changes in both natural killer cell expression of TNF-α ($P = .005$) and natural killer T-cell expression of TNF-α ($P = .04$). These findings of reduced inflammation were significantly correlated with increases in lower body strength ($r = -.69$, $P < .001$; $r = -.36$, $P = .04$ for TNF-α on natural killer cells and natural killer T cells, respectively), suggesting that resistance training may have a beneficial effect on the inflammatory profile in breast cancer survivors as a result of improvements in muscular strength/muscle mass.[74]

Although some studies have found no changes in inflammatory markers due to an exercise intervention, other studies have. Janelsins et al assessed the effects of a 12-week moderately intense Tai Chi Chuan (traditional Chinese martial art) intervention on breast cancer survivors. Posttreatment patients with breast cancer were randomized into the Tai Chi

Table 1. Study descriptions and outcomes of commonly examined inflammatory markers in breast cancer survivors.

STUDY	PARTICIPANTS AND RANDOMIZATION	EXERCISE INTERVENTION	NO. OF PARTICIPANTS INCLUDED IN ANALYSES	MEAN AGE (SD)	INFLAMMATORY MARKER CHANGES
Fairey et al.[71,72]	Postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy (with or without current tamoxifen or anastrozole therapy use) were randomized to either an exercise or control group	Supervised exercise group trained on recumbent or upright cycle ergometers 3×/wk for 15 wk for duration of 15 to 35 min at approx. 70% to 75% of peak oxygen consumption	Overall = 52; Exercise = 24, Control = 28	Overall = 59 (6); Exercise = 59 (5), Control = 58 (6)	*Mean between group change in CRP was –1.49 mg/L between the exercise and control groups from baseline to week 15, only approaching significance ($P = .066$)
Hutnick et al.[60]	Breast cancer survivors following chemotherapy were assigned to either a formal exercise intervention or no formal exercise intervention	Met with a trainer or at-home exercise 3×/wk for 6 mo. Resistance training using Flexbands (4 upper and lower body exercises, 1-3 sets, 8-12 reps) and aerobic activity (60%-75% functional capacity). Total session time was 40 to 90 min	Overall = 49; Exercise = 28, Control = 21	Overall = not reported; Exercise = 48.5 (10.6), Control = 52.3 (9.2)	*No significant changes in plasma IL-6 concentrations were found over time for either group
Payne et al.[73]	Postmenopausal breast cancer survivors receiving hormonal treatment with tamoxifen, anastrozole, or letrozole were randomized to a walking exercise intervention or usual care	A prescribed home-based walking exercise intervention: moderate walking activity, 20 min in duration, 4×/wk for 14 wk	Overall = 20; Exercise = 10, Control = 10	Overall = 64.7 (6.3); Exercise = not reported, Control = not reported	*No significant differences were found in serum IL-6 levels between groups or over time from baseline to week 12
Gómez et al.[53]	Postmenopausal breast cancer survivors who were 2-5 years posttreatment (consisting of surgery with axillary lymphadenectomy and both postsurgery radiotherapy and chemotherapy) were randomized to a training group or usual care control group	A combined (aerobic + strength) 8-wk exercise training intervention. 3×/wk individually supervised sessions, 90 min duration each. Resistance training: varied 1 to 3 sets, resistance that allowed 8 to 15 reps (8-15 repetition maximum), targeting large and small muscle groups; Aerobic training: 20 to 30 min on a cycle ergometer at 70% to 80% of maximal heart rate	Overall = 16; Exercise = 8, Control = 8	Overall = 50 (5); Exercise = not reported, Control = not reported	*No significant changes were found for various blood cytokine levels from pre- to postexercise in both groups *There was a tendency for an interaction (group × time) effect to reach statistical significance in the IL-10/TNF-α ratio ($P = .064$)

Table 1. (Continued)

STUDY	PARTICIPANTS AND RANDOMIZATION	EXERCISE INTERVENTION	NO. OF PARTICIPANTS INCLUDED IN ANALYSES	MEAN AGE (SD)	INFLAMMATORY MARKER CHANGES
Hagstrom et al.[74]	Breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy were randomized to either a resistance training intervention group or non-exercise control group	Resistance training was conducted 3×/wk for 16 wk. Each exercise was performed for 3 sets of 8 to 10 reps at approx. 80% of the 1 repetition maximum. Sessions lasted 60 min	Overall = 39; Exercise = 20, Control = 19	Overall = 51.9 (8.8); Exercise = 51.2 (8.5), Control = 52.7 (9.4)	*No significant changes between groups were observed for serum levels of CRP, IL-6, IL-10, or TNF-α
Janelsins et al.[70]	Breast cancer survivors who had completed treatment between 1 and 30 mo previously were randomly assigned to either a Tai Chi Chuan group or a psychosocial support therapy control group	A moderate-intensity Tai Chi Chuan intervention, sessions lasting 60 min 3×/wk for 12 wk. The intervention was instructor led, each session consisted of a 15-move short form of Yang-Style Tai Chi Chuan	Overall = 19; Exercise = 9, Control = 10	Overall = 53; Exercise = 54.3 (10.6), Control = 52.7 (6.7)	*No significant differences between groups at postintervention in serum levels of IL-6 or IL-2 *Changes in fat-free mass were positively correlated with changes in serum IL-6 ($r = .474$, $P = .040$) and negatively correlated with changes in serum IL-2 ($r = -.491$, $P = .038$) *In addition, changes in fat mass were negatively correlated with changes in serum IL-6 ($r = -.505$, $P = .028$) and positively correlated with changes in serum IL-2 ($r = .552$, $P = .018$)
Jones et al.[62]	Postmenopausal breast cancer survivors who had completed adjuvant treatment (except endocrine therapy) at least 6 mo before enrollment were randomized to either an aerobic exercise intervention or usual care	Participants were instructed to complete 150 min of moderate-intensity aerobic exercise, consisting of 3×/wk trainer-supervised sessions and 2×/wk unsupervised sessions for 6 mo. Exercise ranged from 50% to 80% of predicted maximal heart rate	Overall = 67; Exercise = 36, Control = 31	Overall = 56; Exercise = 56.4 (9.6), Control = 55.4 (7.6)	*After 6 mo, plasma concentrations of IL-6, CRP, and TNF-α did not differ between groups *Secondary analyses showed a significant reduction in IL-6 ($P < .01$) among exercisers who exercised at least 120 min/wk (IL-6 ↓ 14.29%) compared with those who exercised <120 min/wk (IL-6 ↑ 18.54%) *There was also a borderline significant correlation between change in percent body fat and change in CRP in the exercise group ($r = .27$, $P = .069$)

Abbreviations: CRP, C-reactive protein; IL-2, interleukin 2; IL-6, interleukin 6; IL-10, interleukin 10; TNF-α, tumor necrosis factor α.

Chuan exercise group or a psychosocial support therapy control group. Subjects in the Tai Chi Chuan group met for 60 minutes 3 times per week. Breast cancer survivors who participated in the Tai Chi Chuan were found to have nonsignificant decreases in IL-6 along with nonsignificant increases in IL-2. The researchers found that changes in fat-free mass were positively correlated with changes in IL-6 and negatively correlated with changes in IL-2. As fat-free mass increased, IL-6 also increased but IL-2 decreased. This lead the authors to believe that the elevated IL-6 levels were positive markers of the reduction in fat mass that resulted from the moderate-intensity form of exercise.[70]

A total of 68 breast cancer survivors were randomized into either a 6-month aerobic exercise intervention (n = 36) or usual care (n = 32) in a study conducted by Jones et al. At baseline, the study found that both IL-6 and CRP were positively correlated with percent body fat, body weight, and BMI, and inversely correlated with pedometer steps per day. These results suggest that IL-6 and CRP were associated with higher adiposity as well as lower levels of physical activity at baseline. After 6 months, plasma concentrations of IL-6, CRP, and TNF-α did not differ between the exercise and usual care groups. However, secondary analyses showed a significant decrease in IL-6 among exercisers who exercised at least 120 minutes per week compared with those who exercised less than 120 minutes per week. The authors also reported a borderline significant correlation between change in percent body fat and change in CRP in women randomized to exercise ($P = .069$). Poor adherence to the exercise intervention may have affected the results because women who met at least 80% of the exercise goal showed significant decreases in IL-6. The authors concluded by stating potential mechanisms through which physical activity may reduce inflammation. These mechanisms include the following: anti-inflammatory cytokine release during exercise, effects of muscle-derived IL-6, reductions in adipose tissue, and inhibition of TNF-α production by epinephrine.[62]

Meneses-Echávez et al performed a systematic review with meta-analysis on multiple studies examining different types of exercise on inflammatory mediators in breast cancer survivors. They were able to find that exercise significantly reduced the serum concentrations of IL-6 in breast cancer survivors using data from eight trials. In addition, their meta-regression analysis found significant linear interactions between the exercise intervention length (>11 weeks) and duration (>45 min/session) with changes in IL-6 levels. There were also significant decreases found in the levels of TNF-α from data taken from six trials, which may be related to reductions in adipose tissue with exercise. It should be noted that there was a significant benefit observed for IL-2; however, data were taken from only two studies that evaluated this cytokine. The authors went on to hypothesize that long-term exercise may improve the most common symptom of breast cancer survivors, fatigue, by counteracting key mediators of low-grade inflammation such as IL-6 in women with breast cancer.[75]

Conclusions

Overview of the gaps in the current literature and exercise prescription guidelines for cancer survivors

The role chronic inflammation plays in the development of cancer, progression, likelihood of recurrence, and survival is widely recognized.[75] Although there are specific risks related to cancer treatments that need to be considered when survivors exercise, there seems to be consistent evidence that exercise is safe and well tolerated without adverse effects in breast cancer survivors.[76] Few studies have examined markers of inflammation in breast cancer survivors, and even fewer studies have investigated the inflammatory response to exercise in this population.[52] Also, most of these studies are generally small, and the evidence is not consistent.[77] In general, there are minimal studies examining the effects exercise has on biomarkers in patients with breast cancer or survivors that would help in understanding the mechanisms affecting the relationship between physical activity and cancer prognosis. It is difficult to determine whether the type or dose of exercise affects inflammatory markers differently because studies are inadequate.[14]

Most of the studies that have explored the relationship between exercise and markers of inflammation in breast cancer survivors have only focused on the inflammatory response due to long-term exercise interventions in these patients. Most exercise oncology studies have only observed pre- and postlevels of inflammatory markers in response to an exercise intervention and not the effect of an acute bout of exercise on these markers in breast cancer survivors. It is necessary to observe the magnitude and temporal response of cytokines to understand the inflammatory response to exercise. Exercise prescriptions for breast cancer survivors are modeled after those for healthy populations.[76] Findings are currently inconclusive whether breast cancer survivors have similar exercise-induced inflammatory responses as healthy individuals. The acute effects of exercise need to be explored to examine the more direct relationship between exercise and the role of inflammation in breast cancer survivors. Understanding the more acute effects of exercise may allow for the enhancement of exercise prescription guidelines, as well as the time course needed before prescribing the next exercise session. This auxiliary understanding will be helpful in order for these patients to fully recover and receive the maximal health benefits of exercise without increasing the risk of further illness.

There are multiple limitations in the current literature regarding the effect of exercise on inflammatory markers in breast cancer survivors. There is a lack of objective measures of physical activity, such as accelerometers, across observational studies examining physical activity and disease outcome in this

population. Many of the inconsistencies found between studies may be due to the wide range of disease stages as well as the various treatments for patients with breast cancer.[75] Also, the modalities (type) of physical activity have been very diverse from study to study ranging from aerobic to resistance, combinations of both, and even nontraditional exercise interventions, such as tai chi. In addition to different doses of exercise employed from study to study, there are also different intensities of exercise interventions, all resulting in nongeneralizable findings for the inflammatory response. Furthermore, these different methods used to assess physical activity in different studies make it difficult to extrapolate specific recommendations from the findings regarding the exact/optimal type, dose, and timing of physical activity required to reduce mortality or positively improve the inflammatory profile after a cancer diagnosis.[14] Future research should focus on determining a prescription of physical activity that yields clinically significant changes for primary inflammatory markers in breast cancer survivors.

Author Contributions

All manuscript activities were completed by RCM.

Disclosures and Ethics

Because this manuscript is a narrative review summarizing results throughout the literature, approval from ethics committees and consent from participating patients are not needed.

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